09/659,737
60/155029

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=> d his

     (FILE 'HOME' ENTERED AT 14:58:05 ON 25 MAR 2004)

     FILE 'MEDLINE, EMBASE, BIOSIS, BIOTECHDS, SCISEARCH, HCAPLUS, NTIS,
     LIFESCI' ENTERED AT 14:58:32 ON 25 MAR 2004
L1             8 S "MLK4"
L2             0 S "JNKKKK"
L3            19 S "JNKKK"
L4           132 S "C-JUN TERMINAL KINASE"
L5           151 S L3 OR L4
L6       6441791 S CLON? OR EXPRESS? OR RECOMBINANT
L7            74 S L5 AND L6
L8            33 DUP REM L7 (41 DUPLICATES REMOVED)
                 E BLUMENBERG M/AU
L9           448 S E3
                 E GAZEL A M/AU
L10            1 S E3
L11          448 S L9 OR L10
L12            1 S L7 AND L11
L13            4 DUP REM L1 (4 DUPLICATES REMOVED)
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NEWS 4	DEC 08	INPADOC: Legal Status data reloaded
NEWS 5	SEP 29	DISSABS now available on STN
NEWS 6	OCT 10	PCTFULL: Two new display fields added
NEWS 7	OCT 21	BIOSIS file reloaded and enhanced
NEWS 8	OCT 28	BIOSIS file segment of TOXCENTER reloaded and enhanced
NEWS 9	NOV 24	MSDS-CCOHS file reloaded
NEWS 10	DEC 08	CABA reloaded with left truncation
NEWS 11	DEC 08	IMS file names changed
NEWS 12	DEC 09	Experimental property data collected by CAS now available in REGISTRY
NEWS 13	DEC 09	STN Entry Date available for display in REGISTRY and CA/CAplus
NEWS 14	DEC 17	DGENE: Two new display fields added
NEWS 15	DEC 18	BIOTECHNO no longer updated
NEWS 16	DEC 19	CROPU no longer updated; subscriber discount no longer available
NEWS 17	DEC 22	Additional INPI reactions and pre-1907 documents added to CAS databases
NEWS 18	DEC 22	IFIPAT/IFIUDB/IFICDB reloaded with new data and search fields
NEWS 19	DEC 22	ABI-INFORM now available on STN
NEWS 20	JAN 27	Source of Registration (SR) information in REGISTRY updated and searchable
NEWS 21	JAN 27	A new search aid, the Company Name Thesaurus, available in CA/CAplus
NEWS 22	FEB 05	German (DE) application and patent publication number format changes
NEWS 23	MAR 03	MEDLINE and LMEDLINE reloaded
NEWS 24	MAR 03	MEDLINE file segment of TOXCENTER reloaded
NEWS 25	MAR 03	FRANCEPAT now available on STN

NEWS EXPRESS	MARCH 5 CURRENT WINDOWS VERSION IS V7.00A, CURRENT MACINTOSH VERSION IS V6.0b(ENG) AND V6.0Jb(JP), AND CURRENT DISCOVER FILE IS DATED 3 MARCH 2004
NEWS HOURS	STN Operating Hours Plus Help Desk Availability
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FILE 'HOME' ENTERED AT 14:58:05 ON 25 MAR 2004

=> file medline embase biosis biotechds scisearch hcaplus ntis lifesci
COST IN U.S. DOLLARS                                  SINCE FILE      TOTAL
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FILE 'LIFESCI' ENTERED AT 14:58:32 ON 25 MAR 2004
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=> s "MLK4"
L1            8 "MLK4"

=> s "JNKKKK"
L2            0 "JNKKKK"

=> s "JNKKK"
L3           19 "JNKKK"

=> s "c-Jun terminal kinase"
L4          132 "C-JUN TERMINAL KINASE"

=> s l3 or l4
L5          151 L3 OR L4

=> s clon? or express? or recombinant
   5 FILES SEARCHED...
L6      6441791 CLON? OR EXPRESS? OR RECOMBINANT

=> s l5 and l6
L7           74 L5 AND L6

=> dup rem l7
PROCESSING COMPLETED FOR L7
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L8 33 DUP REM L7 (41 DUPLICATES REMOVED)

=> d 1-33 ibib ab

L8 ANSWER 1 OF 33 MEDLINE on STN DUPLICATE 1
ACCESSION NUMBER: 2004107022 IN-PROCESS
DOCUMENT NUMBER: PubMed ID: 14981264
TITLE: The voltage-gated potassium channel Kv1.3 regulates peripheral insulin sensitivity.
AUTHOR: Xu Jianchao; Wang Peili; Li Yanyan; Li Guoyong; Kaczmarek Leonard K; Wu Yanling; Koni Pandelakis A; Flavell Richard A; Desir Gary V
CORPORATE SOURCE: Department of Medicine,Yale University School of Medicine, and Veterans Affairs Medical Center, New Haven, CT, USA.
CONTRACT NUMBER: DK48105B (NIDDK)
K08DK02917 (NIDDK)
R21DK064317 (NIDDK)
SOURCE: Proceedings of the National Academy of Sciences of the United States of America, (2004 Mar 2) 101 (9) 3112-7. Journal code: 7505876. ISSN: 0027-8424.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: IN-PROCESS; NONINDEXED; Priority Journals
ENTRY DATE: Entered STN: 20040304
Last Updated on STN: 20040320

AB Kv1.3 is a voltage-gated potassium (K) channel **expressed** in a number of tissues, including fat and skeletal muscle. Channel inhibition improves experimental autoimmune encephalitis, in part by reducing IL-2 and tumor necrosis factor production by peripheral T lymphocytes. Gene inactivation causes mice (Kv1.3-/-) exposed to a high-fat diet to gain less weight and be less obese than littermate control. Interestingly, although Kv1.3-/- mice on the high-calorie diet gain weight, they remain euglycemic, with low blood insulin levels. This observation prompted us to examine the effect of Kv1.3 gene inactivation and inhibition on peripheral glucose homeostasis and insulin sensitivity. Here we show that Kv1.3 gene deletion and channel inhibition increase peripheral insulin sensitivity in vivo. Baseline and insulin-stimulated glucose uptake are increased in adipose tissue and skeletal muscle of Kv1.3-/- mice. Inhibition of Kv1.3 activity facilitates the translocation of the glucose transporter, GLUT4, to the plasma membrane. It also suppresses **c -JUN terminal kinase** activity in fat and skeletal muscle and decreases IL-6 and tumor necrosis factor secretion by adipose tissue. We conclude that Kv1.3 inhibition improves insulin sensitivity by increasing the amount of GLUT4 at the plasma membrane. These results pinpoint a pathway through which K channels regulate peripheral glucose homeostasis, and identify Kv1.3 as a pharmacologic target for the treatment of diabetes.

L8 ANSWER 2 OF 33 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
ACCESSION NUMBER: 2004:52996 BIOSIS
DOCUMENT NUMBER: PREV200400056156
TITLE: Oxidative stress induces nucleo-cytoplasmic translocation of pancreatic transcription factor PDX-1 through activation of c-Jun NH2-terminal kinase.
AUTHOR(S): Kawamori, Dan; Kajimoto, Yoshitaka; Kaneto, Hideaki [Reprint Author]; Umayahara, Yutaka; Fujitani, Yoshio; Miyatsuka, Takeshi; Watada, Hirotaka; Leibiger, Ingo B.; Yamasaki, Yoshimitsu; Hori, Masatsugu
CORPORATE SOURCE: Department of Internal Medicine and Therapeutics, Graduate School of Medicine, Osaka University, 2-2 Yamadaoka, A8, Suita City, Osaka Pref., 565-0871, Japan
kaneto@medone.med.osaka-u.ac.jp
SOURCE: Diabetes, (December 2003) Vol. 52, No. 12, pp. 2896-2904.

print.
ISSN: 0012-1797 (ISSN print).
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 21 Jan 2004
Last Updated on STN: 21 Jan 2004

AB Oxidative stress is induced in pancreatic beta-cells under diabetic conditions and causes beta-cell dysfunction. Anti-oxidant treatment of diabetic animals leads to recovery of insulin biosynthesis and increases the **expression** of its controlling transcription factor, pancreatic duodenal homeobox-1 (PDX-1), in pancreatic beta-cells. Here, we show that PDX-1 is translocated from the nuclei to the cytoplasm of pancreatic beta-cells in response to oxidative stress. When oxidative stress was charged upon beta-cell-derived HIT-T15 cells, both endogenous PDX-1 and exogenously introduced green fluorescent protein-tagged PDX-1 moved from the nuclei to the cytoplasm. The addition of a dominant negative form of c-Jun NH2-terminal kinase (JNK) inhibited oxidative stress-induced PDX-1 translocation, suggesting an essential role of JNK in mediating this phenomenon. Whereas the nuclear localization signal (NLS) in PDX-1 was not affected by oxidative stress, leptomycin B, a specific inhibitor of the classical leucine-rich nuclear export signal (NES), inhibited nucleo-cytoplasmic translocation of PDX-1 induced by oxidative stress. Moreover, we identified an NES at position 82-94 of the mouse PDX-1 protein. Thus, our present results revealed a novel mechanism that negatively regulates PDX-1 function. The identification of the NES, which overrides the function of the NLS in an oxidative stress-responsive, JNK-dependent manner, supports the complicated regulation of PDX-1 function in vivo and may further the understanding of beta-cell pathophysiology in diabetes.

L8 ANSWER 3 OF 33 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
ACCESSION NUMBER: 2003:475848 BIOSIS
DOCUMENT NUMBER: PREV200300475848
TITLE: Pomegranate fruit extract could be a novel agent for cancer chemoprevention: Studies in mouse skin.
AUTHOR(S): Afaq, Farrukh [Reprint Author]; Saleem, Mohammad [Reprint Author]; Brans, Richard [Reprint Author]; Mukhtar, Hasan [Reprint Author]
CORPORATE SOURCE: University of Wisconsin, Madison, WI, USA
SOURCE: Proceedings of the American Association for Cancer Research Annual Meeting, (July 2003) Vol. 44, pp. 950. print.
Meeting Info.: 94th Annual Meeting of the American Association for Cancer Research. Washington, DC, USA. July 11-14, 2003.
ISSN: 0197-016X.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 15 Oct 2003
Last Updated on STN: 15 Oct 2003

L8 ANSWER 4 OF 33 MEDLINE on STN DUPLICATE 2
ACCESSION NUMBER: 2003446483 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12736137
TITLE: G alpha 13-mediated transformation and apoptosis are permissively dependent on basal ERK activity.
AUTHOR: Adarichev Vyacheslav A; Vaiskunaite Rita; Niu Jiaxin; Balyasnikova Irina V; Voyno-Yasenetskaya Tatyana A
CORPORATE SOURCE: Department of Pharmacology, University of Illinois, Chicago, IL 60612, USA.
CONTRACT NUMBER: GM-56159 (NIGMS)
GM-65160 (NIGMS)
SOURCE: American journal of physiology. Cell physiology, (2003 Oct) 285 (4) C922-34.

Journal code: 100901225. ISSN: 0363-6143.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200310
ENTRY DATE: Entered STN: 20030926
Last Updated on STN: 20031024
Entered Medline: 20031023

AB We previously reported that the alpha-subunit of heterotrimeric G13 protein induces either mitogenesis and neoplastic transformation or apoptosis in a cell-dependent manner. Here, we analyzed which signaling pathways are required for G alpha 13-induced mitogenesis or apoptosis using a novel mutant of G alpha 13. We have identified that in human cell line LoVo, the mutation encoding substitution of Arg260 to stop codon in mRNA of G alpha 13 subunit produced a mutant protein (G alpha 13-T) that lacks a COOH terminus and is endogenously **expressed** in LoVo cells as a polypeptide of 30 kDa. We found that G alpha 13-T lost its ability to promote proliferation and transformation but retained its ability to induce apoptosis. We found that full-length G alpha 13 could stimulate Elk1 transcription factor, whereas truncated G alpha 13 lost this ability. G alpha 13-dependent stimulation of Elk1 was inhibited by dominant-negative extracellular signal-regulated kinase (MEK) but not by dominant-negative MEKK1. Similarly, MEK inhibitor PD-98059 blocked G alpha 13-induced Elk1 stimulation, whereas JNK inhibitor SB-203580 was ineffective. In Rat-1 fibroblasts, G alpha 13-induced cell proliferation and foci formation were also inhibited by dominant-negative MEK and PD-98059 but not by dominant-negative MEKK1 and SB-203580. Whereas G alpha 13-T alone did not induce transformation, coexpression with constitutively active MEK partially restored its ability to transform Rat-1 cells. Importantly, full-length but not G alpha 13-T could stimulate Src kinase activity. Moreover, G alpha 13-dependent stimulation of Elk1, cell proliferation, and foci formation were inhibited by tyrosine kinase inhibitor, genistein, or by dominant-negative Src kinase, suggesting the involvement of a Src-dependent pathway in the G alpha 13-mediated cell proliferation and transformation. Importantly, truncated G alpha 13 retained its ability to stimulate apoptosis signal-regulated kinase ASK1 and **c-Jun terminal kinase**, JNK. Interestingly, the apoptosis induced by G alpha 13-T was inhibited by dominant-negative ASK1 or by SB-203580.

L8 ANSWER 5 OF 33 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
ACCESSION NUMBER: 2004:69975 BIOSIS
DOCUMENT NUMBER: PREV200400070603
TITLE: Regulation of ERK/JNK/p70S6K in two rat models of liver injury and fibrosis.
AUTHOR(S): Svegliati-Baroni, Gianluca [Reprint Author]; Ridolfi, Francesco; Caradonna, Zaira; Alvaro, Domenico; Marzioni, Marco; Saccomanno, Stefania; Candelaresi, Cinzia; Trozzi, Luciano; Macarri, Giampiero; Benedetti, Antonio; Folli, Franco
CORPORATE SOURCE: Clinica di Gastroenterologia, Universita di Ancona, Ospedale Regionale Torrette, Via Conca, 60020, Ancona, Italy
g.svegliati@univpm.it
SOURCE: Journal of Hepatology, (October 2003) Vol. 39, No. 4, pp. 528-537. print.
ISSN: 0168-8278 (ISSN print).
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 4 Feb 2004
Last Updated on STN: 4 Feb 2004

AB Background/Aims: The regulation of three major intracellular signalling protein kinases was investigated in two models of liver injury leading to

hepatic fibrosis, dimethylnitrosamine administration (DMN) and bile duct ligation (BDL). Methods: Extracellular signal-regulated kinases (ERK)1/2, **c-Jun terminal kinase** (JNK) and p70S6-kinase (p70S6K) were studied in vivo in the whole liver, in liver sections and in isolated hepatocytes, cholangiocytes and hepatic stellate cells (HSC). Results: In the whole liver, activation of these kinases occurred with a different kinetic pattern in both models of liver injury. By immunohistochemistry and Western blot in isolated cells, phosphorylated kinases were detected in proliferating cells (i.e. hepatocytes and cholangiocytes after DMN and BDL, respectively), in addition to stellate-like elements. ERK1/2, JNK and p70S6K activation was associated with hepatocytes proliferation after DMN, while JNK activation was not associated with cholangiocytes proliferation after BDL. In HSC isolated from injured livers, protein kinases were differentially activated after BDL and DMN. Kinases activation in HSC in vivo preceded cell proliferation and alpha-smooth muscle actin appearance, a marker of HSC transformation in myofibroblast-like cells, and collagen deposition. Conclusions: Our findings indicate that these kinases are coordinately regulated during liver regeneration and suggest that their modulation could be considered as a future therapeutic approach in the management of liver damage.

L8 ANSWER 6 OF 33 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
ACCESSION NUMBER: 2003:347018 BIOSIS
DOCUMENT NUMBER: PREV200300347018
TITLE: Disruption of the actin cytoskeleton results in nuclear factor-kappa B activation and inflammatory mediator production in human intestinal epithelial cells.
AUTHOR(S): Hasko, Gyorgy [Reprint Author]; Nemeth, Zoltan H.; Deitch, Edwin A.; Davidson, Marson T.; Szabo, Csaba
CORPORATE SOURCE: Department of Surgery, University of Medicine and Dentistry New Jersey, 185 South Orange Avenue, Newark, NJ, 07103-2714, USA
haskoge@umdnj.edu; nemethzo@umdnj.edu; edeitch@umdnj.edu; mdavidson@umdnj.edu; szabocsaba@aol.com
SOURCE: FASEB Journal, (March 2003) Vol. 17, No. 4-5, pp. Abstract No. 866.33. http://www.fasebj.org/. e-file.
Meeting Info.: FASEB Meeting on Experimental Biology: Translating the Genome. San Diego, CA, USA. April 11-15, 2003. FASEB.
ISSN: 0892-6638 (ISSN print).
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 30 Jul 2003
Last Updated on STN: 30 Jul 2003

AB The cytoskeleton in eukaryotic cells is composed of microtubules and the actin cytoskeleton. The microtubule system has recently emerged as an important regulator of NF-kB function. However, the role that the actin microfilament system plays in controlling NF-kB activation is incompletely understood. In this study, we examined the effect of actin cytoskeleton disruption on NF-kB activation in human intestinal epithelial cells. Treatment of HT-29 or Caco-2 cells with the prototypic actin disrupting agent cytochalasin D resulted in increased NF-kB DNA binding and NF-kB-dependent transcriptional activity. This NF-kB activation by cytochalasin D was secondary to an effect on IkB. That is because cytochalasin D induced IkB degradation and the cytochalasin D-induced increase in NF-kB dependent transcriptional activity was prevented by a dominant negative IkB mutant. Exposure of the cells to the cytochalasins D or B, as well as another actin disrupting agent, latrunculin B, increased gene **expression** and release of the NF-kB-dependent chemokines IL-8 and GRO-a.. Cytochalasin D also activated p38 mitogen activated protein kinase and **c-jun terminal kinase**, which pathways contributed to the cytochalasin D-induced

increase in IL-8 production. These results demonstrate that the actin cytoskeleton plays an important role regulating NF-kB activation and inflammatory events in intestinal epithelial cells.

L8 ANSWER 7 OF 33 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
ACCESSION NUMBER: 2002:292166 BIOSIS
DOCUMENT NUMBER: PREV200200292166
TITLE: Pathways of induction of peroxiredoxin I **expression** in osteoblasts. Roles of p38 mitogen-activated protein kinase and protein kinase C.
AUTHOR(S): Li, Baojie; Ishii, Tetsuro; Tan, Choon Ping; Soh, Jae-Won; Goff, Stephen P. [Reprint author]
CORPORATE SOURCE: Dept. of Biochemistry and Molecular Biophysics, College of Physicians and Surgeons, Columbia University, 701 W. 168th St., HHSC1128, New York, NY, 100322, USA goff@cuccfa.ccc.columbia.edu
SOURCE: Journal of Biological Chemistry, (April 5, 2002) Vol. 277, No. 14, pp. 12418-12422. print.
CODEN: JBCHA3. ISSN: 0021-9258.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 15 May 2002
Last Updated on STN: 15 May 2002

AB Peroxiredoxin I (Prx I) is an oxidative stress-inducible antioxidant protein with thioredoxin peroxidase activity. Here we report that the levels of Prx I mRNA and protein are dramatically increased in a murine osteoblast cell line, MC3T3-E1, by treatment with sodium arsenate. We further studied the signaling pathways that control the induction of Prx I **expression**. The treatment of osteoblasts with arsenate activated ERK1/2, JNK, and p38 MAPK. Pre-treating cells with inhibitors of p38 MAPK abolished the induction of Prx I protein but had minimal effect on the induction of Prx I mRNA, suggesting that p38 MAPK activity was required for post-transcriptional regulation. The inhibition of ERK1 and ERK2 had no effect on the induction of Prx I **expression**. Furthermore, rottlerin, an inhibitor of protein kinase Cdelta (PKCdelta) and calmodulin kinase III, abrogated the up-regulation at both protein and mRNA levels. Staurosporine and Go6983, inhibitors for PKC, also inhibited the induction of Prx I, suggesting that protein kinase Cdelta is required for the induction by arsenate. PKCdelta was activated by arsenate treatment by in vitro kinase assays. The inhibition of PKCdelta by rottlerin did not affect the activation of p38 MAPK by arsenate. These results suggest that there are two separate signaling pathways involved in the up-regulation of Prx I protein in response to arsenate, PKCdelta required for transcriptional activation and p38 MAPK required for post-transcriptional regulation.

L8 ANSWER 8 OF 33 MEDLINE on STN DUPLICATE 3
ACCESSION NUMBER: 2002437966 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12187281
TITLE: Activation of mitogen activated protein kinases and apoptosis of germ cells after vasectomy in the rat.
AUTHOR: Shiraishi Koji; Yoshida Ken-Ichi; Fujimiya Tatsuya; Naito Katsusuke
CORPORATE SOURCE: Departments of Urology and Legal Medicine, Yamaguchi University School of Medicine, Yamaguchi, Japan.
SOURCE: Journal of urology, (2002 Sep) 168 (3) 1273-8.
Journal code: 0376374. ISSN: 0022-5347.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 200209
ENTRY DATE: Entered STN: 20020829
Last Updated on STN: 20020919

Entered Medline: 20020918

AB PURPOSE: Vasectomy induces a large amount of germ cell apoptosis. We examined the activation of mitogen activated protein kinases (MAPKs) in association with the apoptosis and proliferation of germ cells after vasectomy in the rat. MATERIALS AND METHODS: Eight-week-old Wistar rats underwent bilateral vasectomy and the testes were harvested 1 to 9 days after vasectomy. Germ cell apoptosis was evaluated by terminal deoxynucleotidyl transferase mediated deoxyuridine triphosphate nick end labeling and electrophoretic assay of DNA fragmentation. Western blotting and immunohistochemistry were used to examine the temporal and spatial activation of signal regulated kinases 1/2, **c-Jun-terminal kinases** 1/2 and p38. Phospho-specific MAPK antibodies were used to examine their activations. Proliferation of germ cells was evaluated by proliferative nuclear cell antigen **expression**. RESULTS: Germ cell apoptosis was detected predominantly in primary spermatocytes with a peak 7 days after vasectomy. Signal regulated kinases 1/2, **c-Jun-terminal kinases** 1/2 and p38 were constitutively **expressed** in the control testis. Western blotting and immunohistochemistry showed rapid activation of signal regulated kinases 1/2, followed by activation of **c-Jun-terminal kinases** 1/2 and p38. Immunohistochemical study demonstrated the temporal and spatial relationships of apoptosis and MAPK activation in primary spermatocytes. On the other hand, proliferating cell nuclear antigen **expression** was enhanced in tetraploid spermatocyte and spermatogonia maximally 5 days after vasectomy. CONCLUSIONS: MAPKs were rapidly activated after vasectomy and germ cell apoptosis was observed after vasectomy. In contrast to the delayed phase up to 24 weeks after vasectomy, we observed hyperdynamic cellular turnover, spermatocyte loss through apoptosis and enhanced germ cell proliferation transiently at the early phase after vasectomy.

L8 ANSWER 9 OF 33 MEDLINE on STN DUPLICATE 4

ACCESSION NUMBER: 2002661945 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12421372
TITLE: Identification of JNK-dependent and -independent components of cerebellar granule neuron apoptosis.
AUTHOR: Harris Charles; Maroney Anna C; Johnson Eugene M Jr
CORPORATE SOURCE: Department of Molecular Biology, Washington University School of Medicine, St Louis, Missouri 63110, USA.
CONTRACT NUMBER: R01NS38651 (NINDS)
R37AG-12947 (NIA)
SOURCE: Journal of neurochemistry, (2002 Nov) 83 (4) 992-1001.
Journal code: 2985190R. ISSN: 0022-3042.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200212
ENTRY DATE: Entered STN: 20021108
Last Updated on STN: 20021227
Entered Medline: 20021224

AB Cerebellar granule neurons grown in high potassium undergo rapid apoptosis when switched to medium containing 5 mm potassium, a stimulus mimicking deafferentation. This cell death can be blocked by genetic deletion of Bax, a member of the pro-apoptotic Bcl-2 family, cycloheximide an inhibitor of macromolecular synthesis or **expression** of dominant-negative c-jun. These observations suggest that Bax activation is the result of c-jun target gene(s) up-regulation following trophic withdrawal. Candidate genes include the BH3-only Bcl-2 family members Dp5 and Bim. The molecular mechanisms underlying granule cell neuronal apoptosis in response to low potassium were investigated using CEP-1347 (KT7515), an inhibitor of the MLK family of **JNKKK**. CEP-1347 provided protection of potassium-serum-deprived granule cells, but such

neuroprotection was not long term. The incomplete protection was not due to incomplete blockade of the JNK signaling pathway because c-jun phosphorylation as well as induction of c-jun RNA and protein were completely blocked by CEP-1347. Following potassium-serum deprivation the JNKK MKK4 becomes phosphorylated, an event blocked by CEP-1347. Cells that die in the presence of CEP-1347 activate caspases; and dual inhibition of caspases and MLKs has additive, not synergistic, effects on survival. A lack of synergism was also seen with the p38 inhibitor SB203580, indicating that the neuroprotective effect of the JNK pathway inhibitor cannot be explained by p38 activation. Activation of the JNK signaling pathway seems to be a key event in granule cell apoptosis, but these neurons cannot survive long term in the absence of sustained PI3 kinase signaling.

L8 ANSWER 10 OF 33 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2002:257567 HCAPLUS
DOCUMENT NUMBER: 137:184256
TITLE: Joint damage and inflammation in c-Jun N-terminal kinase 2 knockout mice with passive murine collagen-induced arthritis
AUTHOR(S): Han, Zuoning; Chang, Lufen; Yamanishi, Yuji; Karin, Michael; Firestein, Gary S.
CORPORATE SOURCE: University of California San Diego School of Medicine, La Jolla, CA, 92093, USA
SOURCE: Arthritis & Rheumatism (2002), 46(3), 818-823
CODEN: ARHEAW; ISSN: 0004-3591
PUBLISHER: Wiley-Liss, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Previous studies have demonstrated that inhibition of c-Jun N-terminal kinase (JNK) decreases joint destruction in the rat adjuvant arthritis model. The present study was undertaken to investigate whether selective loss of JNK-2 function decreases joint destruction in JNK-2 knockout mice, in order to determine the role of this isoform in inflammatory arthritis. Passive collagen-induced arthritis (CIA) was induced in Jnk2-/- and wild-type mice by administering anti-type II collagen antibodies. Arthritis was assessed daily using a semiquant. clin. scoring system. Fibroblast-like synoviocytes (FLS) were prepared from Jnk2-/- and wild-type mice, and JNK protein **expression** was determined by Western blot anal. Matrix metalloproteinase 13 (MMP-13) **expression** was determined by Northern blot anal., and activator protein 1 (AP-1) binding activity by electromobility shift assay (EMSA). The JNK protein level in Jnk2-/- mice with CIA was 22% of that in wild-type mice with CIA ($P < 0.001$), and mainly the 46-kd isoform was **expressed** in the former group. Surprisingly, clin. arthritis was slightly more severe in the Jnk2-/- mice. Histol. scores for synovial inflammation were not significantly different. However, Safranin O-stained sections from the Jnk2-/- mice exhibited significantly less joint damage. Although joint destruction was decreased in Jnk2-/- mice with CIA, EMSA and Northern blot anal. of total joint exts. revealed similar levels of AP-1 binding and MMP-13 **expression** in Jnk2-/- and wild-type mice. The lack of correlation with AP-1 activity and MMP **expression** was probably because non-FLS cells in the joint may **express** more JNK-1 than do FLS. JNK-2 is a determinant of matrix degradation, but it has little effect on inflammation in arthritis. Complete inhibition of MMP **expression** and joint destruction will likely require combined JNK-1 and JNK-2 inhibition.
REFERENCE COUNT: 15 THERE ARE 15 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 11 OF 33 MEDLINE on STN DUPLICATE 5
ACCESSION NUMBER: 2002400327 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12149148
TITLE: An anti-GD2 monoclonal antibody enhances apoptotic effects

of anti-cancer drugs against small cell lung cancer cells via JNK (**c-Jun terminal kinase**) activation.

AUTHOR: Yoshida Shoko; Kawaguchi Haruhiko; Sato Shigeki; Ueda Ryuzo; Furukawa Koichi

CORPORATE SOURCE: Department of Biochemistry II, Nagoya University School of Medicine, Showa-ku, Nagoya 466-0065, Japan.

SOURCE: Japanese journal of cancer research : Gann, (2002 Jul) 93 (7) 816-24.
Journal code: 8509412. ISSN: 0910-5050.

PUB. COUNTRY: Japan

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 200308

ENTRY DATE: Entered STN: 20020801
Last Updated on STN: 20021212
Entered Medline: 20030822

AB Small cell lung cancer (SCLC) cell lines specifically **express** ganglioside GD2, and anti-GD2 monoclonal antibodies (mAbs) caused suppression of cell growth and induced apoptosis of SCLC cells with single use. Here, enhancement of the cytotoxic effects of various anti-cancer drugs with an anti-GD2 mAb was demonstrated. The cytotoxicity of all six drugs examined was markedly enhanced, i.e. 2.4 - 7.8-fold increase of cell sensitivity in terms of IC(50). In particular, the combination of cisplatin (CDDP) with an anti-GD2 mAb resulted in prominent enhancement of cytotoxicity even in low - moderate GD2-**expressing** lines. The anti-GD2 mAb induced weak activation of **c-Jun terminal kinase** (JNK) in SCLC cells, and all anti-cancer drugs also induced its activation to various degrees. When CDDP and an anti-GD2 mAb were used together, significantly stronger JNK activation was observed corresponding to the cytotoxic effects, suggesting that synergistic phosphorylation of JNK with two reagents induced prominent apoptosis. The essential role of JNK in the induction of SCLC apoptosis with CDDP and anti-GD2 mAb was confirmed by experiments with a JNK inhibitor, curcumin. These results suggest that anti-GD2 mAbs would be very efficient in combination with anti-cancer drugs, both to achieve SCLC-specific cytotoxicity and to enhance its magnitude.

L8 ANSWER 12 OF 33 MEDLINE on STN

ACCESSION NUMBER: 2002096084 MEDLINE

DOCUMENT NUMBER: PubMed ID: 11825878

TITLE: Activation of the JNK pathway during dorsal closure in Drosophila requires the mixed lineage kinase, slipper.

AUTHOR: Stronach Beth; Perrimon Norbert

CORPORATE SOURCE: Department of Genetics, Howard Hughes Medical Institute, Harvard Medical School, Boston, Massachusetts 02115, USA.

CONTRACT NUMBER: GM19775 (NIGMS)

SOURCE: Genes & development, (2002 Feb 1) 16 (3) 377-87.
Journal code: 8711660. ISSN: 0890-9369.

PUB. COUNTRY: United States

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 200202

ENTRY DATE: Entered STN: 20020205
Last Updated on STN: 20020301
Entered Medline: 20020228

AB The Jun kinase (JNK) pathway has been characterized for its role in stimulating AP-1 activity and for modulating the balance between cell growth and death during development, inflammation, and cancer. Six families of mammalian kinases acting at the level of **JNKKK** have emerged as upstream regulators of JNK activity (MLK, LZK, TAK, ASK, MEKK, and TPL); however, the specificity underlying which kinase is utilized for

transducing a distinct signal is poorly understood. In Drosophila, JNK signaling plays a central role in dorsal closure, controlling cell fate and cell sheet morphogenesis during embryogenesis. Notably, in the fly genome, there are single homologs of each of the mammalian **JNKKK** families. Here, we identify mutations in one of those, a mixed lineage kinase, named slipper (slpr), and show that it is required for JNK activation during dorsal closure. Furthermore, our results show that other putative **JNKKKs** cannot compensate for the loss of slpr function and, thus, may regulate other JNK or MAPK-dependent processes.

L8 ANSWER 13 OF 33 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
ACCESSION NUMBER: 2002:440991 BIOSIS
DOCUMENT NUMBER: PREV200200440991
TITLE: Unimpaired activation of c-Jun NH2-terminal kinase (JNK) 1 upon CD40 stimulation in B cells of patients with X-linked agammaglobulinemia.
AUTHOR(S): Brunner, Cornelia [Reprint author]; Kreth, Hans Wolfgang; Ochs, Hans D.; Schuster, Volker
CORPORATE SOURCE: Department of Physiological Chemistry, University of Ulm, Albert-Einstein-Allee 11, D-89081, Ulm, Germany Cornelia.Brunner@medizin.uni-ulm.de
SOURCE: Journal of Clinical Immunology, (July, 2002) Vol. 22, No. 4, pp. 244-251. print.
CODEN: JCIMDO. ISSN: 0271-9142.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 14 Aug 2002
Last Updated on STN: 14 Aug 2002

AB X-linked agammaglobulinemia (XLA) is caused by mutations in the gene encoding the cytoplasmic Bruton's tyrosine kinase (Btk). Btk has been shown to play an essential role in the development of B1 (CD5+) and conventional circulating mature B cells (B2) in mouse and man. It has been shown in earlier studies that Btk is involved in both the BCR- and CD40-mediated signaling pathways. In this study, we analyzed the responsiveness of Epstein-Barr virus (EBV) transformed B cells from nine XLA patients to CD40 stimulation, particularly the CD40 induced activation of c-Jun N-terminal kinase (JNK). In eight XLA patients the JNK activation was unimpaired and in one case JNK could not be activated by anti-CD40 stimulation. Btk protein **expression** was detectable by Western blotting in six cases, in one case Btk **expression** was drastically reduced, and in three cases no Btk **expression** could be observed. Btk kinase activity was found in three cases and it was reduced in one and not detectable in five cases. Furthermore, in one female patient with an agammaglobulinemia, Btk **expression** and function as well as JNK activation by CD40 stimulation was unimpaired. Our findings demonstrate that JNK activation via the CD40 signaling pathway is intact in EBV-transformed B cells of most if not all XLA patients, independent of the mutation and its effect on Btk **expression** and kinase activity. We suggest that Btk is not necessary for the activation of JNK upon CD40 stimulation, at least in the B cell subpopulation we had studied. We cannot exclude that these B cells belong to a "leaky" B-cell subpopulation in which the CD40 signaling pathway has become independent of Btk function.

L8 ANSWER 14 OF 33 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
ACCESSION NUMBER: 2002:362809 BIOSIS
DOCUMENT NUMBER: PREV200200362809
TITLE: Intrinsic P-glycoprotein **expression** in multicellular prostate tumor spheroids is regulated by reactive oxygen species.
AUTHOR(S): Wartenberg, M. [Reprint author]; Ling, F. C. [Reprint author]; Schallenberg, M. [Reprint author]; Baeumer, A. T. [Reprint author]; Petrat, K. [Reprint author]; Hescheler, J. [Reprint author]; Sauer, H. [Reprint author]

CORPORATE SOURCE: Department of Neurophysiology, University of Cologne, Robert-Koch-Str. 39, D-50931, Cologne, Germany
SOURCE: Pfluegers Archiv European Journal of Physiology, (March, 2002) Vol. 443, No. Supplement 1, pp. S212. print. Meeting Info.: 81st Annual Joint Meeting of the Physiological Society, the Scandinavian Physiological Society and the German Physiological Society. Tuebingen, Germany. March 15-19, 2002. CODEN: PFLABK. ISSN: 0031-6768.
DOCUMENT TYPE: Conference; (Meeting) Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 3 Jul 2002 Last Updated on STN: 3 Jul 2002

L8 ANSWER 15 OF 33 BIOTECHDS COPYRIGHT 2004 THOMSON DERWENT/ISI on STN
ACCESSION NUMBER: 2001-08201 BIOTECHDS
TITLE: New polynucleotides encoding a c-Jun N-terminal kinase kinase kinases i.e. MLK4, PAK4, associated with skin damage for use in drug screening and development; vector-mediated gene transfer, **expression** in host cell, antisense oligonucleotide and ribozyme for **recombinant** protein production and disease gene therapy
AUTHOR: Blumenberg M; Gazel A M
PATENT ASSIGNEE: Univ.New-York
LOCATION: New York, NY, USA.
PATENT INFO: EP 1085093 21 Mar 2001
APPLICATION INFO: EP 2000-307866 12 Sep 2000
PRIORITY INFO: US 1999-155029 20 Sep 1999
DOCUMENT TYPE: Patent
LANGUAGE: English
OTHER SOURCE: WPI: 2001-236883 [25]
AB The human DNA sequences as defined by protein sequences of the: MLK4 gene containing 54 amino acids (I); PAK4 gene containing 48 amino acids (II); PAK5 gene containing 48 amino acids (III), 311 amino acids (IV) or 681 amino acids (V); and the YSK gene containing 48 amino acids (VI) (all specified), are claimed. Also claimed are: a **recombinant** vector containing (I-VI) or derivatives of (I-VI); a host cell containing the vector; a substantially purified or isolated protein (VII) containing a protein sequence selected from (I-VI); preparation of (VII) by culturing the host cell under conditions that allow **expression** of the protein and recovering the protein; an antibody specific to a protein containing (I-VI); screening compounds (e.g. antisense oligonucleotides or ribozymes) that affect the cellular levels of c-Jun N-terminal kinase kinase kinase (**JNKKK**) gene product; screening compounds that affect the activity of a **JNKKK**; identifying a binding partner of YSK2; and detection of an MLK4-, PAK4-, PAK5- or YSK2-related DNA in a sample. The new DNA sequences encoding a **JNKKK** protein, which is associated with skin damage is useful in drug screening. (51pp)

L8 ANSWER 16 OF 33 MEDLINE on STN
ACCESSION NUMBER: 2001404946 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11438574
TITLE: Dishevelled regulates the metabolism of amyloid precursor protein via protein kinase C/mitogen-activated protein kinase and **c-Jun terminal kinase**.
AUTHOR: Mudher A; Chapman S; Richardson J; Asuni A; Gibb G; Pollard C; Killick R; Iqbal T; Raymond L; Varndell I; Sheppard P; Makoff A; Gower E; Soden P E; Lewis P; Murphy M; Golde T E; Rupniak H T; Anderton B H; Lovestone S
CORPORATE SOURCE: Departments of Neuroscience and Psychiatry, Institute of

Psychiatry, King's College London, London SE5 8AF, United Kingdom.
SOURCE: Journal of neuroscience : official journal of the Society for Neuroscience, (2001 Jul 15) 21 (14) 4987-95. Journal code: 8102140. ISSN: 1529-2401.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200107
ENTRY DATE: Entered STN: 20010730
Last Updated on STN: 20021218
Entered Medline: 20010726

AB Alzheimer's disease (AD) is a disorder of two pathologies: amyloid plaques, the core of which is a peptide derived from the amyloid precursor protein (APP), and neurofibrillary tangles composed of highly phosphorylated tau. Protein kinase C (PKC) is known to increase non-amyloidogenic alpha-secretase cleavage of APP, producing secreted APP (sAPPalpha), and glycogen synthase kinase (GSK)-3beta is known to increase tau phosphorylation. Both PKC and GSK-3beta are components of the wnt signaling cascade. Here we demonstrate that overexpression of another member of this pathway, dishevelled (dvl-1), increases sAPPalpha production. The dishevelled action on APP is mediated via both **c-jun terminal kinase** (JNK) and protein kinase C (PKC)/mitogen-activated protein (MAP) kinase but not via p38 MAP kinase. These data position dvl-1 upstream of both PKC and JNK, thereby explaining the previously observed dual signaling action of dvl-1. Furthermore, we show that human dvl-1 and wnt-1 also reduce the phosphorylation of tau by GSK-3beta. Therefore, both APP metabolism and tau phosphorylation are potentially linked through wnt signaling.

L8 ANSWER 17 OF 33 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
ACCESSION NUMBER: 2001:100647 BIOSIS
DOCUMENT NUMBER: PREV200100100647
TITLE: Insulin-like growth factor-1 protects H9c2 cardiac myoblasts from oxidative stress-induced apoptosis via phosphatidylinositol 3-kinase and extracellular signal-regulated kinase pathways.
AUTHOR(S): Hong, Feng; Kwon, Si Joong; Jhun, Bong Sook; Kim, Sung Soo; Ha, Joohun; Kim, Soo-Ja; Sohn, Nak Won; Kang, Chulhun; Kang, Insug [Reprint author]
CORPORATE SOURCE: Department of Molecular Biology, School of Medicine, Kyung Hee University, 1 Hoegi-dong, Dongdaemun-gu, Seoul, 130-701, South Korea
iskang@nms.kynghee.ac.kr
SOURCE: Life Sciences, (January 26, 2001) Vol. 68, No. 10, pp. 1095-1105. print.
CODEN: LIFSAK. ISSN: 0024-3205.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 21 Feb 2001
Last Updated on STN: 15 Feb 2002

AB Oxidative stress plays a critical role in cardiac injuries during ischemia/reperfusion. Insulin-like growth factor-1 (IGF-1) promotes cell survival in a number of cell types, but the effect of IGF-1 on the oxidative stress has not been elucidated in cardiac muscle cells. Therefore, we examined the role of IGF-1 signaling pathway in cell survival against H2O2-induced apoptosis in H9c2 cardiac myoblasts. H2O2 treatment induced apoptosis in H9c2 cells, and pretreatment of cells with IGF-1 suppressed apoptotic cell death. The antiapoptotic effect of IGF-1 was blocked by LY294002 (an inhibitor of phosphatidylinositol 3-kinase) and by PD98059 (an inhibitor of extracellular signal-regulated kinase (ERK)). The protective effect of IGF-1 was also blocked by rapamycin (an inhibitor of p70 S6 kinase). Furthermore, H9c2 cells stably transfected

with constitutively active PI 3-kinase (H9c2-p110*) and Akt (H9c2-Gag-Akt) constructs were more resistant to H2O2 cytotoxicity than control cells. Although H2O2 activates both p38 mitogen-activated protein kinase (MAPK) and c-Jun N-terminal kinase (JNK), IGF-1 inhibited only JNK activation. Activated PI 3-kinase (H9c2-p110*) and pretreatment of cells with IGF-1 down-regulated Bax protein levels compared to control cells. Taken together, our results suggest that IGF-1 transmits a survival signal against oxidative stress-induced apoptosis in H9c2 cells via PI 3-kinase and ERK-dependent pathways and the protective effect of IGF-1 is associated with the inhibition of JNK activation and Bax **expression**.

L8 ANSWER 18 OF 33 MEDLINE on STN DUPLICATE 7
ACCESSION NUMBER: 2001186677 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11274246
TITLE: Polycystin: new aspects of structure, function, and regulation.
AUTHOR: Wilson P D
CORPORATE SOURCE: Mount Sinai School of Medicine, 1425 Madison Avenue, New York, NY 10029, USA.. pat.wilson@mssm.edu
SOURCE: Journal of the American Society of Nephrology : JASN, (2001 Apr) 12 (4) 834-45. Ref: 89
Journal code: 9013836. ISSN: 1046-6673.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200107
ENTRY DATE: Entered STN: 20010723
Last Updated on STN: 20010723
Entered Medline: 20010719

AB Polycystin-1 is a modular membrane protein with a long extracellular N-terminal portion that bears several ligand-binding domains, 11 transmembrane domains, and a > or =200 amino acid intracellular C-terminal portion with several phosphorylation signaling sites. Polycystin-1 is highly **expressed** in the basal membranes of ureteric bud epithelia during early development of the metanephric kidney, and disruption of the PKD1 gene in mice leads to cystic kidneys and embryonic or perinatal death. It is proposed that polycystin-1 functions as a matrix receptor to link the extracellular matrix to the actin cytoskeleton via focal adhesion proteins. Co-localization, co-sedimentation, and co-immunoprecipitation studies show that polycystin-1 forms multiprotein complexes with alpha2beta1-integrin, talin, vinculin, paxillin, p130cas, focal adhesion kinase, and c-src in normal human fetal collecting tubules and sub-confluent epithelial cultures. In normal adult kidneys and confluent epithelial cultures, polycystin-1 is downregulated and forms complexes with the cell-cell adherens junction proteins E-cadherin and beta-, gamma-, and alpha-catenin. Polycystin-1 activation at the cell membrane leads to intracellular signaling via phosphorylation through the **c-Jun terminal kinase** and wnt pathways leading to activation of AP-1 and TCF/LEF-dependent genes, respectively. The C-terminal of polcystin-1 has been shown to be phosphorylated by c-src at Y4237, by protein kinase A at S4252, and by focal adhesion kinase and protein kinase X at yet-to-be identified residues. Inhibition of tyrosine phosphorylation or increased cellular calcium increases polycystin-1 focal adhesion complexes versus polycystin-1 adherens junction complexes, whereas disruption of the actin cytoskeleton dissociates all polycystin-1 complexes. Genetic evidence suggests that PKD1, PKD2, NPHP1, and tensin are in the same pathway.

L8 ANSWER 19 OF 33 MEDLINE on STN DUPLICATE 8
ACCESSION NUMBER: 2001487063 MEDLINE

DOCUMENT NUMBER: PubMed ID: 11529938
TITLE: Sulphasalazine inhibits macrophage activation: inhibitory effects on inducible nitric oxide synthase **expression**, interleukin-12 production and major histocompatibility complex II **expression**.
AUTHOR: Hasko G; Szabo C; Nemeth Z H; Deitch E A
CORPORATE SOURCE: Department of Surgery, UMD-New Jersey Medical School, Newark, NJ 07103, USA.. haskoge@umdnj.edu
SOURCE: Immunology, (2001 Aug) 103 (4) 473-8.
Journal code: 0374672. ISSN: 0019-2805.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200109
ENTRY DATE: Entered STN: 20010903
Last Updated on STN: 20011001
Entered Medline: 20010927

AB The anti-inflammatory agent sulphasalazine is an important component of several treatment regimens in the therapy of ulcerative colitis, Crohn's disease and rheumatoid arthritis. Sulphasalazine has many immunomodulatory actions, including modulation of the function of a variety of cell types, such as lymphocytes, natural killer cells, epithelial cells and mast cells. However, the effect of this agent on macrophage (M phi) function has not been characterized in detail. In the present study, we investigated the effect of sulphasalazine and two related compounds - sulphapyridine and 5-aminosalicylic acid - on M phi activation induced by bacterial lipopolysaccharide (LPS) and interferon-gamma (IFN-gamma). In J774 M phi stimulated with LPS (10 microg/ml) and IFN-gamma (100 U/ml), sulphasalazine (50-500 microM) suppressed nitric oxide (NO) production in a concentration-dependent manner. The **expression** of the inducible NO synthase (iNOS) was suppressed by sulphasalazine at 500 microM. Sulphasalazine inhibited the LPS/IFN-gamma-induced production of both interleukin-12 (IL-12) p40 and p70. The suppression of both NO and IL-12 production by sulphasalazine was superior to that by either sulphapyridine or 5-aminosalicylic acid. Although the combination of LPS and IFN-gamma induced a rapid **expression** of the active forms of p38 and p42/44 mitogen-activated protein kinases and **c-Jun terminal kinase**, sulphasalazine failed to interfere with the activation of any of these kinases. Finally, sulphasalazine suppressed the IFN-gamma-induced **expression** of major histocompatibility complex class II. These results demonstrate that the M phi is an important target of the immunosuppressive effect of sulphasalazine.

L8 ANSWER 20 OF 33 MEDLINE on STN DUPLICATE 9
ACCESSION NUMBER: 2001200195 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11287182
TITLE: The role of the Drosophila TAK homologue dTAK during development.
AUTHOR: Mihaly J; Kockel L; Gaengel K; Weber U; Bohmann D; Mlodzik M
CORPORATE SOURCE: EMBL, Developmental Biology Programme, Meyerhofstrasse 1, 69117, Heidelberg, Germany.
SOURCE: Mechanisms of development, (2001 Apr) 102 (1-2) 67-79.
Journal code: 9101218. ISSN: 0925-4773.
PUB. COUNTRY: Ireland
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200108
ENTRY DATE: Entered STN: 20010820
Last Updated on STN: 20010820
Entered Medline: 20010816

AB The TAK kinases belong to the MAPKKK group and have been implicated in a variety of signaling events. Originally described as a TGF-beta activated kinase (TAK) it has, however, subsequently been demonstrated to signal through p38, Jun N-terminal kinase (JNK) and Nemo types of MAP kinases, and the NFkappaB inducing kinase. Despite these multiple proposed functions, the in vivo role of TAK family kinases remains unclear. Here we report the isolation and genetic characterization of the Drosophila TAK homologue (dTAK). By employing overexpression and double-stranded RNA interference (RNAi) techniques we have analyzed its function during embryogenesis and larval development. Overexpression of dTAK in the embryonic epidermis is sufficient to induce the transcription of the JNK target genes decapentaplegic and puckered. Furthermore, overexpression of dominant negative (DN) or wild-type forms of dTAK in wing and eye imaginal discs, respectively, results in defects in thorax closure and ommatidial planar polarity, two well described phenotypes associated with JNK signaling activity. Surprisingly, RNAi and DN-dTAK **expression** studies in the embryo argue for a differential requirement of dTAK during developmental processes controlled by JNK signaling, and a redundant or minor role of dTAK in dorsal closure. In addition, dTAK-mediated activation of JNK in the Drosophila eye imaginal disc leads to an eye ablation phenotype due to ectopically induced apoptotic cell death. Genetic analyses in the eye indicate that dTAK can also act through the p38 and Nemo kinases in imaginal discs. Our results suggest that dTAK can act as a **JNKKK** upstream of JNK in multiple contexts and also other MAPKs in the eye. However, the loss-of-function RNAi studies indicate that it is not strictly required and thus either redundant or playing only a minor role in the context of embryonic dorsal closure.

L8 ANSWER 21 OF 33 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
ACCESSION NUMBER: 2001:574593 BIOSIS
DOCUMENT NUMBER: PREV200100574593
TITLE: Differential **expression** of active, phosphorylation-dependent MAP kinases, MAPK/ERK, SAPK/JNK and p38, and specific transcription factor substrates following quinolinic acid excitotoxicity in the rat.
AUTHOR(S): Ferrer, I. [Reprint author]; Blanco, R.; Carmona, M.
CORPORATE SOURCE: Unitat de Neuropatologia, Servei d'Anatomia Patologica, Hospitalet de Llobregat, Hospital Princeps d'Espanya (Bellvitge), c/ Feixa Llarga sn, 08907, Llobregat, Spain iferrer@sakma.es
SOURCE: Molecular Brain Research, (19 October, 2001) Vol. 94, No. 1-2, pp. 48-58. print.
CODEN: MBREE4. ISSN: 0169-328X.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 12 Dec 2001
Last Updated on STN: 25 Feb 2002

AB Excitotoxicity is considered a major cell death inductor in neurodegeneration. Yet mechanisms involved in cell death and cell survival following excitotoxic insults are poorly understood. **Expression** of active, phosphorylation-dependent mitogen-activated extracellular signal-regulated kinases (MAPK/ERKs), stress activated c-Jun N-terminal kinases (SAPK/JNKs) and p38 kinases, as well as their putative active specific transcriptional factor substrates CREB, Elk-1, ATF-2, c-Myc and c-Jun, have been examined following intracortical injection of the glutamate analogue quinolinic acid (QA). Increased JNKP and p38P immunoreactivity has been found in the core at 1 h following QA injection, whereas increased MAPKP immunoreactivity occurs in neurons and glial cells localised around the lesion and in neurons in remote cortical regions. This is accompanied by strong phosphorylated Ser63 c-Jun (c-JunP) immunoreactivity in the core at 3 h, and by strong phosphorylated CREB, Elk-1 and ATF-2 (CREBP, Elk-1P and ATF-2P) immunoreactivity mainly in neurons around the core at 24 h following QA injection. Examination with the method of in situ end-labelling of nuclear DNA fragmentation has

revealed large numbers of positive cells with no apoptotic morphology in the core at 24 h, thus indicating that JNKP, p38P and c-JunP over-**expression** precedes cell death. In contrast, MAPKP, CREBP, Elk-1P and ATF-2P, but not phosphorylated c-Myc (c-MycP). over-**expression** correlates with cell survival. Examination of cleaved, active caspase-3 has shown specific immunoreactivity restricted to a few hematogenous cells in the area of injection. Since cleaved caspase-3 is not **expressed** by dying cells in the present paradigm, JNKP, p38P and c-JunP **expression** is not associated with caspase-3 activation. The present results demonstrate selective activation of specific MAPK signals which are involved either in cell death or cell survival triggered by excitotoxic insult.

L8 ANSWER 22 OF 33 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
ACCESSION NUMBER: 2002:263716 BIOSIS
DOCUMENT NUMBER: PREV200200263716
TITLE: The apoptosome is a target of Jun kinase in nitric oxide-induced cardiac myocyte apoptosis.
AUTHOR(S): Andreka, Peter [Reprint author]; Dougherty, Christopher [Reprint author]; Slepak, Tatiana I. [Reprint author]; Webster, Keith A. [Reprint author]; Bishopric, Nanette H. [Reprint author]
CORPORATE SOURCE: Univ of Miami Sch of Med, Miami, FL, USA
SOURCE: Circulation, (October 23, 2001) Vol. 104, No. 17 Supplement, pp. II.142. print.
Meeting Info.: Scientific Sessions 2001 of the American Heart Association. Anaheim, California, USA. November 11-14, 2001. American Heart Association.
CODEN: CIRCAZ. ISSN: 0009-7322.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 1 May 2002
Last Updated on STN: 1 May 2002

L8 ANSWER 23 OF 33 MEDLINE on STN DUPLICATE 10
ACCESSION NUMBER: 2000405874 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10906215
TITLE: Hairy leukoplakia: an unusual combination of transforming and permissive Epstein-Barr virus infections.
AUTHOR: Webster-Cyriaque J; Middeldorp J; Raab-Traub N
CORPORATE SOURCE: Lineberger Comprehensive Cancer Center, Department of Dental Ecology, University of North Carolina, Chapel Hill, North Carolina, USA.
CONTRACT NUMBER: DE11644 (NIDCR)
P30HD37260 (NICHD)
T32 A10 7151-21
+
SOURCE: Journal of virology, (2000 Aug) 74 (16) 7610-8.
Journal code: 0113724. ISSN: 0022-538X.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals; AIDS
ENTRY MONTH: 200008
ENTRY DATE: Entered STN: 20000901
Last Updated on STN: 20000901
Entered Medline: 20000818
AB Human herpesviruses are characterized by distinct states of infection. Typically in permissive herpesvirus infection, abundant virus production results in cell lysis. In latent transforming Epstein-Barr virus (EBV) infection, viral proteins that induce cell growth are **expressed**. The immunodeficiency-associated hairy leukoplakia (HLP) lesion is the only pathologic manifestation of permissive EBV infection; however, within HLP,

viral proteins characteristic of latent infection have also been detected. In this study, we further analyzed **expression** of EBV latent genes and investigated their contribution to the unique histologic phenotype of HLP. Coexpression of lytic and transforming viral proteins was detected simultaneously within individual HLP keratinocytes. LMP1 has now been shown to be uniformly **expressed** in the affected tissue, and it is associated and colocalizes with tumor necrosis factor receptor-associated factor (TRAF) signaling molecules. Effects induced by activated TRAF signaling that were detected in HLP included activation of NF-kappaB and **c-Jun terminal kinase** 1 (JNK1) and upregulated **expression** of epidermal growth factor receptor (EGFR), CD40, A20, and TRAFs. This study identifies a novel state of EBV infection with concurrent **expression** of replicative and transforming proteins. It is probable that both replicative and latent proteins contribute to HLP development and induce many of the histologic features of HLP, such as acanthosis and hyperproliferation. In contrast to other permissive herpesvirus infections, **expression** of EBV transforming proteins within the permissively infected HLP tissue enables epithelial cell survival and may enhance viral replication.

L8 ANSWER 24 OF 33 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
ACCESSION NUMBER: 2000:179435 BIOSIS
DOCUMENT NUMBER: PREV200000179435
TITLE: IL-4 regulation of IL-6 production involves Rac/Cdc42- and p38 MAPK-dependent pathways in keratinocytes.
AUTHOR(S): Wery-Zennaro, Sandrine; Zugaza, Jose L.; Letourneur, Martine; Bertoglio, Jacques; Pierre, Josiane [Reprint author]
CORPORATE SOURCE: Faculte de Pharmacie, INSERM U461, 5, Rue J B Clement, 92296, Chatenay-Malabry Cedex, France
SOURCE: Oncogene, (March 16, 2000) Vol. 19, No. 12, pp. 1596-1604. print.
CODEN: ONCNES. ISSN: 0950-9232.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 11 May 2000
Last Updated on STN: 4 Jan 2002

AB The stress-activated pathways leading to activation of p38 MAP kinase (p38 MAPK) and c-jun N-terminal kinases (JNK) have been shown to be activated by pro-inflammatory cytokines, physical and chemical stresses as well as a variety of hematopoietic growth factors. One exception is interleukin (IL)-4, which does not activate this pathway in hematopoietic cell. We report here that in A431, a keratinocytic cell line, IL-4 activates Rac and Cdc42 and their downstream effector p21-activated kinase (PAK). Rac and Cdc42 appear to regulate a protein kinase cascade initiated at the level of PAK and leading to activation of p38 MAPK, since IL-4 stimulates tyrosine phosphorylation of p38 MAPK and increases its catalytic activity. As A431 cells are able to produce IL-6 in response to IL-4 stimulation, we assessed the involvement of p38 MAPK in IL-6 gene **expression**. A pyrimidazole compound, SB203580, a specific inhibitor of p38 MAPK, inhibits production and gene **expression** of IL-6. SB203580 reduced significantly the stability of IL-6 mRNA. Here we provide evidence that p38 MAPK is activated in response to IL-4 and is involved in IL-6 synthesis by stabilizing IL-6 mRNA.

L8 ANSWER 25 OF 33 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
ACCESSION NUMBER: 2000:314958 BIOSIS
DOCUMENT NUMBER: PREV200000314958
TITLE: Vav modulation of the Ras/MEK/ERK signaling pathway plays a role in NFAT activation and CD69 up-regulation.
AUTHOR(S): Villalba, Martin; Hernandez, Jerry; Deckert, Marcel; Tanaka, Yoshihiko; Altman, Amnon [Reprint author]
CORPORATE SOURCE: Division of Cell Biology, La Jolla Institute for Allergy and Immunology, 10355 Science Center Drive, San Diego, CA,

92121, USA
SOURCE: European Journal of Immunology, (June, 2000) Vol. 30, No. 6, pp. 1587-1596. print.
CODEN: EJIMAF. ISSN: 0014-2980.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 26 Jul 2000
Last Updated on STN: 7 Jan 2002

AB Vav is **expressed** exclusively in hematopoietic cells and becomes phosphorylated on tyrosine in response to antigen receptor ligation. Although Vav can act as a Rac-specific guanine nucleotide exchange factor in vitro and as a c-Jun N-terminal kinase (JNK) activator in ectopic **expression** systems, its physiological functions in lymphocytes remain unclear. Indirect evidence suggests that Vav interacts with the Ras/ERK pathway in T cells. Here, we analyzed the effects of Vav on three known downstream targets of Ras, i. e. activation of ERK and NFAT, and up-regulation of the activation antigen CD69. The MEK inhibitor PD90859 inhibited Vav-induced activation of ERK, and Vav- or anti-CD3-induced activation of NFAT, suggesting that MEK and ERK are involved in Vav-mediated NFAT activation. Similarly to Ras, Vav cooperated with constitutively active calcineurin and with ERK to activate NFAT, and was capable of up-regulating CD69 **expression** in T cells. Moreover, these Vav-mediated functions were all inhibited by a dominant negative Ras mutant. Conversely, however, dominant negative Vav did not inhibit NFAT and ERK activation or CD69 **expression** induced by an active Ras mutant. These findings indicate that Ras functions as an important downstream target of Vav in signaling pathways that lead to NFAT and ERK activation, and to CD69 **expression**. Moreover, the finding that Vav- (or Ras-) induced CD69 **expression** was not inhibited by a dominant negative Rac mutant indicates that Vav mediates some Ras-dependent, but Rac-independent, functions in T cells.

L8 ANSWER 26 OF 33 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN
ACCESSION NUMBER: 2000:782295 SCISEARCH
THE GENUINE ARTICLE: 362QX
TITLE: Molecular aspects of arsenic stress
AUTHOR: Bernstam L (Reprint); Nriagu J
CORPORATE SOURCE: UNIV MICHIGAN, SCH PUBL HLTH, DEPT ENVIRONM HLTH SCI, 109 S OBSERV ST, ANN ARBOR, MI 48109 (Reprint)
COUNTRY OF AUTHOR: USA
SOURCE: JOURNAL OF TOXICOLOGY AND ENVIRONMENTAL HEALTH-PART B-CRITICAL REVIEWS, (OCT-DEC 2000) Vol. 3, No. 4, pp. 293-322.
Publisher: TAYLOR & FRANCIS LTD, 11 NEW FETTER LANE, LONDON EC4P 4EE, ENGLAND.
ISSN: 1093-7404.
DOCUMENT TYPE: General Review; Journal
FILE SEGMENT: LIFE; AGRI
LANGUAGE: English
REFERENCE COUNT: 168

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Arsenic produces a variety of stress responses in mammalian cells, including metabolic abnormalities accompanied by growth inhibition and eventually apoptosis. Morphological alterations in cells exposed to arsenic often suggest underlying disruption of cytoskeletal structural elements responsible for cellular integrity, shape, and locomotion. However, specifics of the ultrastructural changes produced by arsenic remain poorly understood. Various tissues and organs differ in their sensitivity to arsenic, with the liver and skin being the most studied. Characteristic skin pathology related to arsenic exposure ranges from hyperkeratotic lesions to squamous-cell carcinomas. However, molecular events in the arsenic-exposed skin still remain to be elucidated. Although mutagenicity of arsenic has not been unequivocally established, recent evidence supports the view that oncogenic mutations do occur, and that

only selected enzymes related to DNA replication and repair are affected by arsenic. Sensitivity of the mitotic spindle to arsenic, particularly its organic compounds, underlies the well-documented chromosomal aberrations in arsenic-exposed populations.

Arsenite-induced stress at the molecular level shares many features with the heat shock response. This includes the differential sensitivity of the stress signal pathway elements to the magnitude of the stress, stressor-specific activation of the response elements, and the protective role of the heat shock response. Oxidative stress, the central component of heat shock response, is typical of arsenic-related effects that are, in fact, regarded as the chemical paradigm of heat stress. Similar to heat stress, arsenite induces heat shock proteins (HSPs) of various sizes. The signal cascade triggered by arsenitelike heat stress induces the activity of the mitogen-activated protein (MAP) kinases, extracellular regulated kinase (ERK), **c-jun terminal kinase** (JNK), and p38. Through the JNK and p38 pathways, arsenite activates the immediate early genes c-fos, c-jun, and egr-1, usually activated by various growth factors, cytokines, differentiation signals, and DNA-damaging agents. Like other oxygen radical-producing stressors, arsenic induces nitric oxide production at the level of transcriptional activation along with induction of poly(ADP)-ribosylation, NAD depletion, DNA strand breaks, and formation of micronuclei.

This review presents an overview of current research on molecular aspects of arsenic stress with an emphasis on the tissue-specific events in humans. It deals with current progress on the understanding of the signal transduction pathways and mechanisms underlying the sensitivity of various species, organs, and tissues to arsenic.

L8 ANSWER 27 OF 33 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN

ACCESSION NUMBER: 2001:297551 BIOSIS
DOCUMENT NUMBER: PREV200100297551
TITLE: The humanized anti-CD20 antibody Rituxan induces apoptosis in B-cell chronic lymphocytic leukemia (B-CLL) cells in-vitro and in-vivo, through a p38 MAP-kinase dependent signaling pathway.
AUTHOR(S): Pedersen, Irene M. [Reprint author]; Buhl, Anne-Mette [Reprint author]; Klausen, Pia [Reprint author]; Geisler, Christian H. [Reprint author]; Jurlander, Jesper [Reprint author]
CORPORATE SOURCE: Dept. of Hematology, The Finsens Centre, Rigshospitalet, Copenhagen, Denmark
SOURCE: Blood, (November 16, 2000) Vol. 96, No. 11 Part 1, pp. 163a. print.
Meeting Info.: 42nd Annual Meeting of the American Society of Hematology. San Francisco, California, USA. December 01-05, 2000. American Society of Hematology.
CODEN: BLOOAW. ISSN: 0006-4971.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 20 Jun 2001
Last Updated on STN: 19 Feb 2002

AB Antibodies against CD20 have been shown to induce cell death in B-lymphocytes through three different mechanisms: i) antibody dependent cellular cytotoxicity, ii) complement mediated cellular cytotoxicity and iii) induction of apoptosis. We have demonstrated that the last mechanism is responsible for Rituxan-induced cell death in freshly isolated leukemic cells from patients with B-cell chronic lymphocytic leukemia (B-CLL) (Blood 1999, vol 94, suppl. 1, 120(a)). Rituxan-induced apoptosis is related to: i) activation of the three MAP-kinases ERK, JNK and p38, ii) upregulation of the pro-apoptotic proteins p53 and bax and iii) induction of effector caspase activity. We now report that the induction of apoptosis is dependent on p38 MAP-kinase activity, and provide evidence to suggest that a similar mechanism is active in-vivo. When B-CLL cells were

cultured in the presence of cross-linked Rituxan and a specific inhibitor of p38 (SB203580), the degree of apoptosis was decreased by a mean of 43% (Range: 26-65%; n=7). SB203580 inhibited p38 kinase activity in-vitro, and completely blocked Rituxan-induced activation of MAPKAP-K2, a kinase immediately downstream of p38. In order to determine if Rituxan also induces apoptosis and MAP-kinase activation in-vivo, we isolated leukemic cells from three patients treated with Rituxan (375 mg/msq) and analysed these cells for Annexin-binding and **expression** of the phosphorylated forms of p38, ERK and JNK. In all three patients, a significant increase in the percentage of Annexin-positive B-cells was observed within 15 minutes after start of the infusion. Concommitantly, an increase in the level of MAP-kinase phosphorylation was observed. Thus, our results demonstrate that Rituxan specifically induces apoptosis in B-CLL cells in-vitro through a p38-dependent signaling pathway. We suggest that a similar mechanism is responsible for the activity of Rituxan in-vivo. Taken together, these results predict that Rituxan may act in synergy with other agents (i.e. topoisomerase-II inhibitors) that induce apoptosis through p38-dependent mechanisms.

L8 ANSWER 28 OF 33 MEDLINE on STN

ACCESSION NUMBER: 2001089858 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10947158
TITLE: Spermine differentially regulates the production of interleukin-12 p40 and interleukin-10 and suppresses the release of the T helper 1 cytokine interferon-gamma.
AUTHOR: Hasko G; Kuhel D G; Marton A; Nemeth Z H; Deitch E A; Szabo C
CORPORATE SOURCE: Inotek Corporation, Beverly, Massachusetts 01915, USA.
CONTRACT NUMBER: RO1-GM 60915 (NIGMS)
SOURCE: Shock (Augusta, Ga.), (2000 Aug) 14 (2) 144-9.
Journal code: 9421564. ISSN: 1073-2322.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200101
ENTRY DATE: Entered STN: 20010322
Last Updated on STN: 20010322
Entered Medline: 20010125

AB Polyamines are endogenous immunomodulatory molecules. Recent studies revealed that polyamines suppress the production of proinflammatory cytokines and nitric oxide. In the present study, we investigated the effect of the polyamines spermine, spermidine, and putrescine on the production of interleukin (IL)-12 p40, IL-10, and interferon (IFN-gamma) in mouse peritoneal macrophages and spleen cell suspensions. Spermine, but not spermidine or putrescine, suppressed, in a concentration-dependent manner, the production of IL-12 p40 by lipopolysaccharide (LPS)-stimulated macrophages. The effect of spermine was post-transcriptional, because steady-state levels of messenger ribonucleic acid (mRNAs) for IL-12 (p35 and p40) were not affected. In contrast to its inhibitory effect on IL-12 p40, spermine (0.3-3 microM) augmented IL-10 production. The down-regulation of IL-12 p40 by spermine was independent of enhancement of IL-10 by this agent, for spermine retained its ability to suppress IL-12 production in peritoneal macrophages obtained from IL-10-deficient mice. The alterations in cytokine production by spermine did not involve an effect on early intracellular pathways of LPS signal transduction, including the p38 or p42/44 mitogen-activated protein kinases, or the **c-jun terminal kinase**. In spleen cell suspensions, spermine suppressed the release of IFN-gamma induced either by LPS or anti-CD3 antibody. In summary, spermine exerts anti-inflammatory effects by suppressing IL-12 and IFN-gamma and by augmenting the production of IL-10.

L8 ANSWER 29 OF 33 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN

ACCESSION NUMBER: 1999:466819 BIOSIS
DOCUMENT NUMBER: PREV199900466819
TITLE: Leukocyte microparticles stimulate endothelial cell cytokine release and tissue factor induction in a JNK1 signaling pathway.
AUTHOR(S): Mesri, Mehdi; Altieri, Dario C. [Reprint author]
CORPORATE SOURCE: Yale University School of Medicine, 295 Congress Ave., BCMM 436B, New Haven, CT, 06536, USA
SOURCE: Journal of Biological Chemistry, (Aug. 13, 1999) Vol. 274, No. 33, pp. 23111-23118. print.
CODEN: JBCHA3. ISSN: 0021-9258.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 9 Nov 1999
Last Updated on STN: 3 May 2000

AB A role of membrane microparticles (MP) released by vascular cells in endothelial cell (EC) activation was investigated. Flow cytofluorimetric analysis of blood samples from normal volunteers revealed the presence of an heterogeneous MP population, which increased by apprx2-fold after inflammatory stimulation with the chemotactic peptide, N-formyl-Met-Leu-Phe (2,799 +- 360 versus 5241 +- 640, p < 0.001). Blood-derived MP stimulated release of EC cytokines interleukin (IL)-6 (377 +- 68 pg/ml) and MCP-1 (1,282 +- 79) and up-regulated de novo **expression** of tissue factor on the EC surface. This was associated with generation of a factor Xa-dependent procoagulant response (2.28 +- 0.56 nM factor Xa/min/104 cells), in a reaction inhibited by a monoclonal antibody to tissue factor. Fluorescent labeling with antibodies to platelet GPIbalpha or leukocyte lactoferrin demonstrated that circulating MP originated from both platelets and leukocytes. However, depletion of platelet MP with an antibodyto GPIbalpha did not reduce EC IL-6 release, and, similarly, MP from thrombin-stimulated platelets did not induce IL-6 release from endothelium. EC stimulation with leukocyte MP did not result in activation of the transcription factor NF-kappaB and was not associated with tyrosine phosphorylation of extracellular signal-regulated protein kinase, ERK1. In contrast, leukocyte MP stimulated a sustained, time-dependent increased tyrosine phosphorylation of apprx46-kDa c-Jun NH2-terminal kinase (JNK1) in EC. These findings demonstrate that circulating leukocyte MP are up-regulated by inflammatory stimulation in vivo and activate a stress signaling pathway in EC, leading to increased procoagulant and proinflammatory activity. This may provide an alternative mechanism of EC activation, potentially contributing to dysregulation of endothelial functions during vascular injury.

L8 ANSWER 30 OF 33 MEDLINE on STN DUPLICATE 11
ACCESSION NUMBER: 1998261450 MEDLINE
DOCUMENT NUMBER: PubMed ID: 9596671
TITLE: T-Cell receptor signaling pathway exerts a negative control on thrombin-mediated increase in [Ca2+]i and p38 MAPK activation in Jurkat T cells: implication of the tyrosine kinase p56Lck.
AUTHOR: Maulon L; Guerin S; Ricci J E; Breittmayer D F; Auberger P
CORPORATE SOURCE: CJF INSERM 96.05, Activation des Cellules Hematopoietiques, Faculte de Medecine, Nice Cedex, France.
SOURCE: Blood, (1998 Jun 1) 91 (11) 4232-41.
Journal code: 7603509. ISSN: 0006-4971.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199806
ENTRY DATE: Entered STN: 19980713
Last Updated on STN: 19980713
Entered Medline: 19980626

AB Activation of the mitogen-activated protein kinase (Erk) and **c-Jun terminal kinase** is a well-documented mechanism for the seven transmembrane spanning receptors. We have previously shown that thrombin stimulation of the T-leukemic cell line Jurkat induced a transient increase in [Ca2+]i and tyrosine phosphorylation of several cellular proteins. Here, we have analyzed p42-44 MAPK, JNK and p38 MAPK activation using Jurkat T-cell lines deficient in either the tyrosine kinase p56Lck (JCaM1) or the tyrosine phosphatase CD45 (J45.01). Our results demonstrate that p56Lck and CD45 exert a negative control on thrombin-induced p38 MAPK activation and [Ca2+]i release in Jurkat cells. Thrombin receptor **expression** was identical on the different cell lines as assessed by FACS analysis. Tyrosine phosphorylation of p38 MAPK was drastically increased after thrombin stimulation of JCaM1 or J45.01 cells, as compared with parental cells (JE6.1). P42-44 MAPK and JNK activity also enhanced after thrombin treatment of JE6.1 and JCaM1 cell lines, whereas basal kinase activity was higher in J45.01 cells and was not further stimulated by thrombin. Thrombin and thrombin receptor agonist peptide-induced [Ca2+]i mobilization paralleled p38 MAPK activation in JCaM1 and J45.01 cells. Moreover, reconstitution of J45.01 and JCaM1 cell lines with either CD45 or Lck is accompanied by restoration of a normal thrombin-induced [Ca2+]i response and p38MAPK phosphorylation. These data show that a component of the T-cell receptor signaling pathway exerts a negative control on thrombin-induced responses in Jurkat T cells. Accordingly, we found that thrombin enhanced tyrosine phosphorylation of p56Lck and decreased p56Lck kinase activity in J45.01 cells. Our results are consistent with a negative role for p56Lck on thrombin-induced [Ca2+]i release and p38 MAPK activation in Jurkat T-cell lines.

L8 ANSWER 31 OF 33 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN

ACCESSION NUMBER: 1998:315209 BIOSIS
DOCUMENT NUMBER: PREV199800315209
TITLE: Activation of mitogen-activated protein kinases (p38-MAPKs, SAPKs/JNKs and ERKs) by the G-protein-coupled receptor agonist phenylephrine in the perfused rat heart.
AUTHOR(S): Lazou, Antigone; Sugden, Peter H. [Reprint author]; Clerk, Angela
CORPORATE SOURCE: NHLI Div., Imperial Coll. Sch. Med., Royal Brompton Campus, Doverhouse St., London SW3 6LY, UK
SOURCE: Biochemical Journal, (June 1, 1998) Vol. 332, No. 2, pp. 459-465. print.
ISSN: 0264-6021.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 22 Jul 1998
Last Updated on STN: 10 Sep 1998

AB We investigated the ability of phenylephrine (PE), an alpha-adrenergic agonist and promoter of hypertrophic growth in the ventricular myocyte, to activate the three best-characterized mitogen-activated protein kinase (MAPK) subfamilies, namely p38-MAPKs, SAPKs/JNKs (i.e. stress-activated protein kinases/c-Jun N-terminal kinases) and ERKs (extracellularly responsive kinases), in perfused contracting rat hearts. Perfusion of hearts with 100 muM PE caused a rapid (maximal at 10 min) 12-fold activation of two p38-MAPK isoforms, as measured by subsequent phosphorylation of a p38-MAPK substrate, **recombinant** MAPK-activated protein kinase 2 (MAPKAPK2). This activation coincided with phosphorylation of p38-MAPK. Endogenous MAPKAPK2 was activated 4-5-fold in these perfusions and this was inhibited completely by the p38-MAPK inhibitor, SB203580 (10 muM). Activation of p38-MAPK and MAPKAPK2 was also detected in non-contracting hearts perfused with PE, indicating that the effects were not dependent on the positive inotropic/chronotropic properties of the agonist. Although SAPKs/JNKs were also rapidly activated, the activation (2-3-fold) was less than that of p38-MAPK. The ERKs were activated by perfusion with PE and the

activation was at least 50% of that seen with 1 muM PMA, the most powerful activator of the ERKs yet identified in cardiac myocytes. These results indicate that, in addition to the ERKs, two MAPK subfamilies, whose activation is more usually associated with cellular stresses, are activated by the Gq/11-protein-coupled receptor (Gq/11PCR) agonist, PE, in whole hearts. These data indicate that Gq/111PCR agonists activate multiple MAPK signalling pathways in the heart, all of which may contribute to the overall response (e.g. the development of the hypertrophic phenotype).

L8 ANSWER 32 OF 33 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
ACCESSION NUMBER: 1997:19015 BIOSIS
DOCUMENT NUMBER: PREV199799318218
TITLE: Activation of a novel calcium-dependent protein-tyrosine kinase: Correlation with c-Jun N-terminal kinase but not mitogen-activated protein kinase activation.
AUTHOR(S): Yu, Hong; Li, Xiong; Marchetto, Gail S.; Dy, Ruth; Hunter, Deborah; Calvo, Benjamin; Dawson, Tom L.; Wilm, Matthias; Anderegg, Robert J.; Graves, Lee M.; Earp, H. Shelton [Reprint author]
CORPORATE SOURCE: Lineberger Comprehensive Cent., Dep. Med. Pharmacol., Univ. North Carolina Chapel Hill Sch. Med., Chapel Hill, NC 27599, USA
SOURCE: Journal of Biological Chemistry, (1996) Vol. 271, No. 47, pp. 29993-29998.
CODEN: JBCHA3. ISSN: 0021-9258.
DOCUMENT TYPE: Article
LANGUAGE: English
OTHER SOURCE: Genbank-U69109
ENTRY DATE: Entered STN: 15 Jan 1997
Last Updated on STN: 11 Feb 1997

AB Many G protein-coupled receptors (e.g. that of angiotensin II) activate phospholipase C-beta, initially increasing intracellular calcium and activating protein kinase C. In the WB and GN4 rat liver epithelial cell lines, agonist-induced calcium signals also stimulate tyrosine phosphorylation and subsequently increase the activity of c-Jun N-terminal kinase (JNK). We have now purified the major calcium-dependent tyrosine kinase (CADTK), and by peptide and nucleic acid sequencing identified it as a rat homologue of human PYK2. CADTK/PYK2 is most closely related to p125-FAK and both enzymes are **expressed** in NM and GN4 cells. Angiotensin II, which only slightly increases p125-FAK tyrosine phosphorylation in GN4 cells, substantially increased CADTK tyrosine autophosphorylation and kinase activity. Agonists for other G protein-coupled receptors (e.g. LPA), or those increasing intracellular calcium (thapsigargin), also stimulated CADTK. In comparing the two rat liver cell lines, GN4 cells exhibited apprx 5-fold greater angiotensin II- and thapsigargin-dependent CADTK activation than WB cells. Although maximal JNK activation by stress-dependent pathways (e.g. UV and anisomycin) was equivalent in the two cell lines, calcium-dependent JNK activation was 5-fold greater in GN4, correlating with CADTK activation. In contrast to JNK the thapsigargin-dependent calcium signal did not activate mitogen-activated protein kinase and Ang II-dependent mitogen-activated protein kinase activation was not correlated with CADTK activation. Finally, while some stress-dependent activators of the JNK pathway (NaCl and sorbitol) stimulated CADTK, others (anisomycin, UV, and TNF-alpha) did not. In summary, cells **expressing** CADTK/PYK2 appear to have two alternative JNK activation pathways: one stress-activated and the other calcium-dependent.

L8 ANSWER 33 OF 33 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
ACCESSION NUMBER: 1996:438043 BIOSIS
DOCUMENT NUMBER: PREV199699151649
TITLE: Rac-1 dependent stimulation of the JNK/SAPK signaling pathway by Vav.

AUTHOR(S): Crespo, Piero; Bustelo, Xose R.; Aaronson, David S.; Coso, Omar A.; Lopez-Barahona, Monica; Barbacid, Mariano; Gutkind, J. Silvio [Reprint author]

CORPORATE SOURCE: Molecular Signaling Unit, Lab. Cellular Dev. and Oncol., Natl. Inst. Dent. Res., Natl. Inst. Health, Bethesda, MD 20892, USA

SOURCE: Oncogene, (1996) Vol. 13, No. 3, pp. 455-460.
CODEN: ONCNES. ISSN: 0950-9232.

DOCUMENT TYPE: Article

LANGUAGE: English

ENTRY DATE: Entered STN: 26 Sep 1996
Last Updated on STN: 26 Sep 1996

AB The protein product of the human vav oncogene, Vav, exhibits a number of structural motifs suggestive of a role in signal transduction pathways, including a leucine-rich region, a plekstrin homology (PH) domain, a cysteine-rich domain, two SH3 regions, an SH2 domain, and a central Dbl homology (DH) domain. However, the transforming pathway(s) activated by Vav has not yet been elucidated. Interestingly, DH domains are frequently found in guanine nucleotide-exchange factors for small GTP-binding proteins of the Ras and Rho families, and it has been recently shown that, whereas Ras controls the activation of mitogen activated kinases (MAPKs), two members of the Rho family of small GTPases, Rac 1 and Cdc42, regulate activity of stress activated protein kinases (SAPKs), also termed **c-jun terminal kinases** (JNKs). The structural similarity between Vav and other guanine nucleotide exchange factors for small GTP-binding proteins, together with the recent identification of biochemical routes specific for members of the Ras and Rho family of GTPases, prompted us to explore whether MAPK or JNK are downstream components of the Vav signaling pathways. Using the COS-7 cell transient **expression** system, we have found that neither Vav nor the product of the vav proto-oncogene, proto-Vav, can enhance the enzymatic activity of a coexpressed, epitope tagged MAPK. On the other hand, we have observed that, whereas proto-Vav can slightly elevate JNK/SAPK activity, oncogenic Vav potently activates JNK/SAPK to an extent comparable to that elicited by two guanine-nucleotide exchange factors for Rho family members, Dbl and Ost. We also show that point mutations in conserved residues within the cysteine rich and DH domains of Vav both prevent its ability to activate JNK/SAPK and render Vav oncogenically inactive. In addition, we found that coexpression of the Rac-1 N17 dominant inhibitory mutant dramatically diminishes JNK/SAPK stimulation by Vav, as well as reduces the focus-forming ability of Vav in NIH3T3 murine fibroblasts. Taken together, these findings provide the first evidence that Rac-1 and JNK are integral components of the Vav signaling pathway.

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=> e blumenberg m/au
E1            4     BLUMENBERG KLAUS DIETER/AU
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E3          448 --> BLUMENBERG M/AU
E4            7     BLUMENBERG M */AU
E5            2     BLUMENBERG M A/AU
E6           13     BLUMENBERG MARTIN/AU
E7            3     BLUMENBERG MIKI/AU
E8            1     BLUMENBERG MIROLSAV/AU
E9           96     BLUMENBERG MIROSLAV/AU
E10           3     BLUMENBERG NOVOSELAC N/AU
E11           3     BLUMENBERG R/AU
E12          66     BLUMENBERG R M/AU

=> s e3
L9          448 "BLUMENBERG M"/AU

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E1           11     GAZEL A/AU
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E7            1      GAZEL ANDRE/AU
E8            2      GAZEL C/AU
E9            1      GAZEL CHARLES/AU
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E12           1      GAZEL FILHO ADERALDO B/AU

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=> s l9 or l10
L11         448 L9 OR L10

=> d his

     (FILE 'HOME' ENTERED AT 14:58:05 ON 25 MAR 2004)

     FILE 'MEDLINE, EMBASE, BIOSIS, BIOTECHDS, SCISEARCH, HCAPLUS, NTIS,
     LIFESCI' ENTERED AT 14:58:32 ON 25 MAR 2004
L1            8 S "MLK4"
L2            0 S "JNKKKK"
L3           19 S "JNKKK"
L4          132 S "C-JUN TERMINAL KINASE"
L5          151 S L3 OR L4
L6      6441791 S CLON? OR EXPRESS? OR RECOMBINANT
L7           74 S L5 AND L6
L8           33 DUP REM L7 (41 DUPLICATES REMOVED)
                E BLUMENBERG M/AU
L9          448 S E3
                E GAZEL A M/AU
L10           1 S E3
L11         448 S L9 OR L10

=> s l7 and l11
L12           1 L7 AND L11

=> d all

L12   ANSWER 1 OF 1  BIOTECHDS COPYRIGHT 2004 THOMSON DERWENT/ISI on STN
AN    2001-08201  BIOTECHDS
TI    New polynucleotides encoding a c-Jun N-terminal kinase kinase kinases
      i.e. MLK4, PAK4, associated with skin damage for use in drug screening
      and development;
         vector-mediated gene transfer, expression in host cell,
         antisense oligonucleotide and ribozyme for recombinant
         protein production and disease gene therapy
AU    Blumenberg M; Gazel A M
PA    Univ.New-York
LO    New York, NY, USA.
PI    EP 1085093 21 Mar 2001
AI    EP 2000-307866 12 Sep 2000
PRAI  US 1999-155029 20 Sep 1999
DT    Patent
LA    English
OS    WPI: 2001-236883 [25]
AB    The human DNA sequences as defined by protein sequences of the: MLK4 gene
      containing 54 amino acids (I); PAK4 gene containing 48 amino acids (II);
      PAK5 gene containing 48 amino acids (III), 311 amino acids (IV) or 681
      amino acids (V); and the YSK gene containing 48 amino acids (VI) (all
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specified), are claimed. Also claimed are: a **recombinant** vector containing (I-VI) or derivatives of (I-VI); a host cell containing the vector; a substantially purified or isolated protein (VII) containing a protein sequence selected from (I-VI); preparation of (VII) by culturing the host cell under conditions that allow **expression** of the protein and recovering the protein; an antibody specific to a protein containing (I-VI); screening compounds (e.g. antisense oligonucleotides or ribozymes) that affect the cellular levels of c-Jun N-terminal kinase kinase kinase (**JNKKK**) gene product; screening compounds that affect the activity of a **JNKKK**; identifying a binding partner of YSK2; and detection of an MLK4-, PAK4-, PAK5- or YSK2-related DNA in a sample. The new DNA sequences encoding a **JNKKK** protein, which is associated with skin damage is useful in drug screening. (51pp)

CC D PHARMACEUTICALS; D3 Peptides and Proteins; D PHARMACEUTICALS; D7 Clinical Genetic Techniques; A GENETIC ENGINEERING AND FERMENTATION; A1 Nucleic Acid Technology

CT **RECOMBINANT** C-JUN N-TERMINAL KINASE KINASE KINASE PREP., VECTOR-MEDIATED GENE TRANSFER, **EXPRESSION** IN HOST CELL, ANTISENSE OLIGONUCLEOTIDE, RIBOZYME, APPL. DRUG SCREENING, DISEASE GENE THERAPY ENZYME RNA ENZYME DNA SEQUENCE PROTEIN SEQUENCE (VOL.20, NO.16)

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=> dup rem l1
PROCESSING COMPLETED FOR L1
L13            4 DUP REM L1 (4 DUPLICATES REMOVED)

=> d 1-4 ibib ab

L13  ANSWER 1 OF 4  HCAPLUS  COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER:         2003:532691  HCAPLUS
DOCUMENT NUMBER:          139:95435
TITLE:                    Modified receptors on cell membranes for the discovery
                          of therapeutic ligands
INVENTOR(S):              Schwartz, Thue W.; Martini, Lene; Heydorn, Arne;
                          Jorgensen, Rasmus
PATENT ASSIGNEE(S):       7TM Pharma A/S, Den.
SOURCE:                   PCT Int. Appl., 122 pp.
                          CODEN: PIXXD2
DOCUMENT TYPE:            Patent
LANGUAGE:                 English
FAMILY ACC. NUM. COUNT:   2
PATENT INFORMATION:

     PATENT NO.        KIND  DATE           APPLICATION NO.   DATE
     ---------------   ----  --------       ---------------   --------
     WO 2003055914      A2   20030710       WO 2002-DK900     20021220
     WO 2003055914      A3   20031023
         W:  AE, AG, AL, AM, AT, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH,
             CN, CO, CR, CU, CZ, CZ, DE, DE, DK, DK, DM, DZ, EC, EE, EE, ES,
             FI, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG,
             KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW,
             MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SK,
             SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM,
             ZW, AM, AZ, BY
         RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG,
             CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL,
             PT, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML,
             MR, NE, SN, TD, TG
PRIORITY APPLN. INFO.:                    DK 2001-1944      A  20011221
                                          DK 2002-113       A  20020122
                                          DK 2002-1043      A  20020703
                                          US 2002-394122P   P  20020703
AB   A drug discovery method is provided for selecting a compound selected from
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the group consisting of a small organic substance, a biopharmaceutical, or an antibody or part thereof. The method comprises the steps of (i) expressing one or more receptors on a cell membrane, such as, e.g., an exterior cell surface of a cell, (ii) contacting one or more expressed receptors with a test compound or a selection of test compds. (libraries), and (iii) selecting one or more compds. based on its ability to bind one or more receptors. The step of expressing the one or more receptors comprises capturing one or more receptors on the exterior cell surface in a conformation that predominantly enables binding or interaction with a ligand, and the conformation that predominantly enables binding or interaction with a ligand is provided by modification of one or more receptors by a method comprising at least one of the following: (a) fusion with any protein which keeps the receptor in the desired conformation such as, e.g. an arrestin, a modified arrestin, a G-protein or a modified G-protein, (b) site-directed mutagenesis, and (c) deletion. The receptors may be captured on the exterior cell surface by at least one of the following: (d) interaction of the receptor with a scaffolding protein, optionally, with a scaffolding protein network and (e) means for blocking receptor internalization, e.g. by co-expression of a mutated dynamin or a modified arrestin or by use of chems. such as, e.g., sucrose and/or Tris. Thus, by coexpressing of either the wild-type receptor or by modifying the receptor by engineering for example a recognition motif for a strong binder into its structure (for example, a PDZ recognition motif at its C-terminal end), and coexpression of this with a scaffolding protein such as PSD-95 or a modified scaffolding protein which interacts with the cytoskeleton at the cell surface or is made to be closely associated with the membrane through a lipid anchor, a high level of surface expression can be ensured, which will benefit its use in the drug discovery process. As a result of the strong tendency of the scaffolding proteins to interact with each other, just the cotransfection with one or more appropriate scaffolding proteins or modified scaffolding protein may also lead to the formation of patches with high local concns of the receptor or modified receptor, which will be highly beneficial in the drug discovery process where they are used initially to select binding mols. The method is exemplified by expression of the NK1 receptor in an agonist high-affinity binding form at the surface of transfected cells through fusion with arrestin or the N-terminal fragment of arrestin.

L13 ANSWER 2 OF 4 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
DUPLICATE 1
ACCESSION NUMBER: 2003:257416 BIOSIS
DOCUMENT NUMBER: PREV200300257416
TITLE: Mutational analysis of the tyrosine kinome in colorectal cancers.
AUTHOR(S): Bardelli, Alberto; Parsons, D. Williams; Silliman, Natalie; Ptak, Janine; Szabo, Steve; Saha, Saurabh; Markowitz, Sanford; Willson, James K. V.; Parmigiani, Giovanni; Kinzler, Kenneth W.; Vogelstein, Bert; Velculescu, Victor E. [Reprint Author]
CORPORATE SOURCE: Howard Hughes Medical Institute and Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, MD, 21231, USA
velculescu@jhmi.edu
SOURCE: Science (Washington D C), (9 May 2003) Vol. 300, No. 5621, pp. 949. print.
ISSN: 0036-8075 (ISSN print).
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 4 Jun 2003
Last Updated on STN: 4 Jun 2003

L13 ANSWER 3 OF 4 BIOTECHDS COPYRIGHT 2004 THOMSON DERWENT/ISI on STN
ACCESSION NUMBER: 2001-08201 BIOTECHDS
TITLE: New polynucleotides encoding a c-Jun N-terminal kinase kinase

kinases i.e. **MLK4**, PAK4, associated with skin damage for use in drug screening and development; vector-mediated gene transfer, expression in host cell, antisense oligonucleotide and ribozyme for recombinant protein production and disease gene therapy

AUTHOR: Blumenberg M; Gazel A M
PATENT ASSIGNEE: Univ.New-York
LOCATION: New York, NY, USA.
PATENT INFO: EP 1085093 21 Mar 2001
APPLICATION INFO: EP 2000-307866 12 Sep 2000
PRIORITY INFO: US 1999-155029 20 Sep 1999
DOCUMENT TYPE: Patent
LANGUAGE: English
OTHER SOURCE: WPI: 2001-236883 [25]

AB The human DNA sequences as defined by protein sequences of the: **MLK4** gene containing 54 amino acids (I); PAK4 gene containing 48 amino acids (II); PAK5 gene containing 48 amino acids (III), 311 amino acids (IV) or 681 amino acids (V); and the YSK gene containing 48 amino acids (VI) (all specified), are claimed. Also claimed are: a recombinant vector containing (I-VI) or derivatives of (I-VI); a host cell containing the vector; a substantially purified or isolated protein (VII) containing a protein sequence selected from (I-VI); preparation of (VII) by culturing the host cell under conditions that allow expression of the protein and recovering the protein; an antibody specific to a protein containing (I-VI); screening compounds (e.g. antisense oligonucleotides or ribozymes) that affect the cellular levels of c-Jun N-terminal kinase kinase kinase (JNKKK) gene product; screening compounds that affect the activity of a JNKKK; identifying a binding partner of YSK2; and detection of an **MLK4**-, PAK4-, PAK5- or YSK2-related DNA in a sample. The new DNA sequences encoding a JNKKK protein, which is associated with skin damage is useful in drug screening. (51pp)

L13 ANSWER 4 OF 4 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
DUPLICATE 3

ACCESSION NUMBER: 2001:504233 BIOSIS
DOCUMENT NUMBER: PREV200100504233
TITLE: Isolation, expression analysis and chromosomal mapping of a novel human kinase gene **MLK4**.
AUTHOR(S): Kvasha, S. M.; Protopopov, A. I.; Zabarovsky, E. R.; Rynditch, A. V.; Kashuba, V. I.
SOURCE: Biopolimery i Kletka, (July-August, 2001) Vol. 17, No. 4, pp. 302-307. print.
CODEN: BIKLEK. ISSN: 0233-7657.
DOCUMENT TYPE: Article
LANGUAGE: Ukrainian
ENTRY DATE: Entered STN: 31 Oct 2001
Last Updated on STN: 23 Feb 2002

AB We have identified a novel human gene **MLK4**. Two alternatively spliced forms of **MLK4**, named MLK4alpha and MLK4beta, have been isolated. The expression of **MLK4** has been detected in pancreas, kidney, liver, lung, brain, placenta and heart. The gene has been mapped to chromosomal band 1q42. The predicted amino acid sequence of **MLK4** is highly related to the amino acid sequence of the members of MLK family, which play an important role in the signal transduction pathways.

=> d his

(FILE 'HOME' ENTERED AT 14:58:05 ON 25 MAR 2004)

FILE 'MEDLINE, EMBASE, BIOSIS, BIOTECHDS, SCISEARCH, HCAPLUS, NTIS, LIFESCI' ENTERED AT 14:58:32 ON 25 MAR 2004
L1 8 S "MLK4"

L2	0	S	"JNKKKK"
L3	19	S	"JNKKK"
L4	132	S	"C-JUN TERMINAL KINASE"
L5	151	S	L3 OR L4
L6	6441791	S	CLON? OR EXPRESS? OR RECOMBINANT
L7	74	S	L5 AND L6
L8	33		DUP REM L7 (41 DUPLICATES REMOVED)
		E	BLUMENBERG M/AU
L9	448	S	E3
		E	GAZEL A M/AU
L10	1	S	E3
L11	448	S	L9 OR L10
L12	1	S	L7 AND L11
L13	4		DUP REM L1 (4 DUPLICATES REMOVED)

	Issue Date	Pages	Document ID
1	20030508	40	US 20030087899 A1
2	20020425	71	US 20020048746 A1
3	20030715	16	US 6593126 B2

	Issue Date	Pages	Document ID	Title
1	20030715	16	US 6593126 B2	Human kinase and polynucleotides encoding the same

	Issue Date	Pages	Document ID	Title
1	20030417	179	US 20030073888 A1	Screening methods used to identify compounds that modulate a response of a cell to ultraviolet radiation exposure
2	20020711	128	US 20020090624 A1	Gene markers useful for detecting skin damage in response to ultraviolet radiation

	L #	Hits	Search Text
1	L1	3	"mlk4"
2	L2	5	"jnkkk"
3	L3	0	"c-jun terminal kinase$2"
4	L4	611232	clon$3 or express$3 or recombinant
5	L5	8	l1 or l2
6	L6	1	l4 same l5
7	L7	248	BLUMENBERG or GAZEL
8	L8	2	l5 and l7